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Drinking Water Criteria Document for Oxamyl (Vydate) (Trade Name)

Dynamac Corp., Rockville, MD

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DRINKING WATER CRITERIA DOCUMENT

FOR

OXAMYL (VYDATE)

Prepared by

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Prepared for

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Washington, DC 20460

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FOREWORD

Section 1412 (b)(3)(A) of the Safe Drinking Water Act, as amended in 1986, requires the Administrator of the Environmental Protection Agency to publish Maximum Contaminant Level Goals (MCLGs) and promulgate National Primary Drinking Water Regulations for each contaminant, which, in the judgment of the Administrator, may have an adverse effect on public health and which is known or anticipated to occur in public water systems. The MCLG is nonenforceable and is set at a level at which no known or anticipated adverse health effects in humans occur and which allows for an adequate margin of safety. Factors considered in setting the MCLG include health effects data and sources of exposure other than drinking water.

This document provides the health effects basis to be considered in establishing the MCLG. To achieve this objective, data on pharmacokinetics, human exposure, acute and chronic toxicity to animals and humans, epidemiology, and mechanisms of toxicity were evaluated. Specific emphasis is placed on literature data providing dose-response information. Thus, while the literature search and evaluation performed in support of this document was comprehensive, only the reports considered most pertinent in the derivation of the MCLG are cited in the document. The comprehensive literature data base in support of this document includes information published up to April 1987; however, more recent data may have been added during the review process.

When adequate health effects data exist, Health Advisory values for less-than-life-time exposures (One-day, Ten-day, and Longer-term, approximately 10% of an individual's lifetime) are included in this document. These values are not used in setting the MCLG, but serve as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur.

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This document was prepared under a contract with the Criteria and Standards Division, Office of Drinking Water, Environmental Protection Agency (U.S. EPA), Washington, DC (James Murphy, Ph.D., Lead Scientist).

I. SUMMARY

Oxamyl, S-methyl N',N'-dimethyl-N-(methylcarbamoyloxy)-l-thiooxamimidate, is the active ingredient found in the insecticide/nematicide Vydate L[®], which contains 24% oxamyl in methanol. Vydate[®] is widely used for control of insects, mites, and nematodes on field crops, fruits, and ornamentals.

Oxamyl is stable in the solid form and relatively stable in aqueous solutions at acidic pH. At alkaline pH, however, oxamyl is rapidly hydrolyzed to an oximino compound. Exposure to light, particularly at low concentrations, results in rapid and extensive decomposition of oxamyl. Decomposition in soils under both aerobic and anaerobic conditions is also rapid and extensive. Field studies indicate that the mobility of oxamyl in soil is limited.

Oxamyl is rapidly absorbed, metabolized, and eliminated by rodents. Rats eliminated greater than 50% of an oral dose of oxamyl in the urine within 3 days of administration. Mice given an intraperitoneal (ip) injection of oxamyl excreted more than 87% of the dose in the urine within 3 days. Relatively small percentages of each dose were found in the feces of rats or mice within 72 hours postadministration. There was little accumulation of oxamyl in the tissues, although appreciable amounts (7 to 12.5%) were found in the skin and hair of two rats within 3 days of dosing. Oxamyl appears to be extensively metabolized after oral or ip administration. The primary metabolites recovered in urine of both rats and mice were methyl N-hydroxy-N',N'-dimethyl-l-thiooxamimidate (DMTU), N,N-dimethyloxamic acid (DMOA), N-methyloxamic acid (MOA), and methyl N-hydroxyN'-methyl-l-thiooxamimidate (MTU). In addition, oxamyl and N,N-dimethyl-l-cyanoformamide (DMCF) were also found in the urine of mice. Oxamyl has been shown to be metabolized by hepatic microsomes via two major pathways. One pathway involves hydrolysis to DMTU, and the second involves

enzymatic conversion via DMCF to DMOA. A third, minor enzymatic process results in partial demethylation of oxamyl and its metabolites.

The major mechanism of toxicity of oxamyl appears to be cholinesterase inhibition. Acute oral, intraperitoneal, or inhalation exposure to lethal doses of oxamyl resulted in typical clinical signs of cholinesterase inhibition prior to death in rats, mice, rabbits, guinea pigs, and dogs. Oxamyl is extremely toxic via oral, intraperitoneal, and inhalation routes of administration; oral LD_{50} values were 2.5 to 3.0 mg/kg in rats, 2.3 to 3.3 mg/kg in mice, and 7 mg/kg in guinea pigs. The insecticide (in solution) has only limited absorption through the skin as evidenced by dermal LD_{50} values of 750 and >1,200 mg/kg in rabbits and rats, respectively.

Treatment with atropine after administration of lethal doses of oxamyl is antidotal in rats due to its competitive binding of acetylcholine receptor sites on postsynaptic membranes.

Oxamyl is also toxic following long-term oral exposure. Although clinical signs of cholinesterase inhibition were not observed, statistically significant decreases in body weight were noted in male and female rats fed 100 ppm in the diet (5.0 mg/kg/day) for 90 days or 2 years. Serum cholinesterase activity was significantly decreased in females fed 150 ppm (7.5 mg/kg/day) after 4 days and in males fed 150 ppm (7.5 mg/kg/day) after 8 days of exposure to oxamyl. No specific target organs were identified. Histopathologic examination revealed no increased incidences of tumors after ingestion of up to 150 ppm (7.5 mg/kg/day) for 2 years in rats.

Similar results were obtained in a 2-year study in mice fed oxamyl in the diet at levels up to 75 ppm (11.25 mg/kg/day). Significant decreases in body

weights were noted in males and females fed 50 ppm (7.5 mg/kg/day). No increases in incidence or type of neoplastic or nonneoplastic lesions were observed in mice fed up to 75 ppm when compared to controls. From the results of the feeding studies, oxamyl was not carcinogenic in rats fed up to 150 ppm or mice fed up to 75 ppm for 2 years. This is supported by negative results of several in vitro genetic toxicity assays.

In 90-day and 2-year feeding studies in beagles, dietary levels of oxamyl up to 150 ppm (3.8 mg/kg/day) did not elicit any changes in body weight, food consumption, clinical signs, hematologic and urinary parameters, or histopathology when compared to controls. Statistically significant increases in serum alkaline phosphatase activity and cholesterol levels were observed in groups fed 150 ppm after 2 years of exposure, suggesting some effect on the liver. This was not supported by histopathologic findings, however.

Although maternal toxicity (significantly decreased body weight) was marked at 100 ppm (5.0 mg/kg/day), oxamyl fed to pregnant rats at levels up to 300 ppm (15 mg/kg/day) was not teratogenic. Oral doses of up to 4 mg/kg/day administered to pregnant rabbits were not teratogenic, although significantly decreased maternal body weights were observed at 2 mg/kg/day.

Developmental toxicity, as evidenced by decreases in the litter size of dams fed oxamyl at 100 ppm (5.0 mg/kg/day) was demonstrated in both one- and three-generation reproduction studies in rats. Decreased growth (significantly decreased body weight) of weanlings from the groups fed 100 ppm was also noted. Similarly, parental toxicity in the form of significantly decreased body weights was observed in both males and females fed 100 ppm. In this study, oxamyl did not affect fertility or elicit increases in the incidences of

variations or malformations of the offspring of dams fed up to 150 ppm (7.5 mg/kg/day).

No suitable data were found in the literature for derivation of the One- and Ten-day Health Advisories (HAs) for oxamyl. A Longer-term HA of 200 ug/L for a 10-kg child was calculated, based on a No-Observed-Adverse-Effect Level (NOAEL) of 2.5 mg/kg/day identified in a 90-day feeding study with rats. This was substituted as a conservative estimate of both the One- and Ten-day HA values. A Drinking Water Equivalent Level (DWEL) of 900 ug/L for a 70-kg adult was developed, based on a NOAEL of 2.5 mg/kg/day identified in a 2-year feeding study with rats. Oxamyl is classified in Group E: Evidence of Non-carcinogenicity for Humans, based on the results of a 2-year feeding study with rats and a 2-year feeding study with mice.

Although no information on the exposure to or toxicity of oxamyl in humans was found in the literature, the results of animal toxicity studies indicate that acute oral, intraperitoneal, or inhalation exposure to lethal doses of oxamyl at 2.3 to 7 mg/kg can cause rapid death in laboratory animals. However, because of the "reversible" nature of oxamyl toxicity owing to its mode of action and the rapid metabolism and elimination of oxamyl and its metabolites, this insecticide appears to have a wide margin of safety.

II. PHYSICAL AND CHEMICAL PROPERTIES

A. GENERAL PROPERTIES

Oxamyl, S-methyl N',N'-dimethyl-N-(methylcarbamoyloxy)-1-thiooxamimidate (CAS No. 23135-22-0), in its pure state, forms colorless crystals with a slight sulfurlike odor and is considered extremely toxic. The compound was introduced by E.I. duPont de Nemours and Company, Inc., as the main active ingredient in the pesticide Vydate®. As a solid, it is stable. In aqueous solutions, it decomposes slowly. This process is accelerated by aeration, sunlight, alkali, or elevated temperatures. A summary of the physical and chemical properties is listed in Table II-1 (Gosselin, 1981; duPont, 1986; U.S. EPA, 1986; Worthing and Walker, 1983; Kennedy, 1986a).

B. PRODUCTION AND USE

E.I. duPont de Nemours and Company, Inc., is the sole producer of oxamyl. Oxamyl is the active ingredient in the insecticide/nematicide Vydate L®. In 1982, production of oxamyl was reported to be 0.4 million pounds/year (0.3 million pounds/year for use as the insecticide and 0.1 million pounds/year for use as the nematicide) (SRI, 1985). Vydate® consists of 24% oxamyl in methanol. In this form, it is classified as a poison B, which is defined as: "a less dangerous poison: substance, liquid, or solid, other than Class A or irritating material, which is known to be so toxic to man as to afford a hazard to health during transportation or which, in the absence of adequate data on human toxicity, is presumed to be toxic to man." It is used to control insects, mites, and/or nematodes on many field crops, fruits, and ornamentals (O'Bannon and Selhime, 1980; French, 1982; Timmer and French, 1979). Application may be by broadcast or band to soils, as a transplant water treatment, or a foliar spray (duPont, 1986;

Table II-1. Physical and Chemical Properties of Oxamyl

Parameters	Value
CAS number	23135-22-0
Synonyms	Thioxamyl; diovamyl; duPont 1410; DPX 1410; Vydate®
Color/form	Clear crystalline solid
Molecular weight	219.3
Melting point	108-110°C
Vapor pressure at 25°C	2.3×10^{-4} mmHg
Specific gravity at 25°C	0.98
Stability	Stable in solid form, and in liquid form at acidic pH
Structure	$ \begin{array}{c} \text{O} \quad \quad \text{O} \\ \parallel \quad \parallel \\ (\text{CH}_3)_2\text{-N-C-C=N-O-C-N-CH}_3 \\ \\ \text{SCH}_3 \end{array} $
Solubility at 25°C	
Water	280 g/L
Acetone	670 g/L
Ethanol	330 g/L
Toluene	10 g/L

SOURCE: Adapted from Worthing and Walker (1983); Kennedy (1986a);
U.S. EPA (1986); duPont (1986); Gosselin (1981).

1986; Kennedy, 1986a). It is registered for use on a variety of vegetation for preplant, at planting, or postplant treatments (Agriculture Research Service, 1986). Some or all applications may be classified by the U.S. EPA as Restricted Use Pesticides (RUP).

C. ENVIRONMENTAL FATE AND EFFECTS

Because oxamyl is applied to a wide variety of crops at different stages of cultivation, the compound inevitably comes into contact with soil and water. Thus, its fate in these media is important.

1. Stability in Water

Harvey and Han (1978a) reported that in water, oxamyl (1,200 ppm) was stable for at least 11 days at pH 5 or lower, but was hydrolyzed rapidly to the oximino compound at pH 9. Peebles (1977) calculated a half-life of approximately 3 days for a 1,200-ppm aqueous solution of oxamyl at pH 9.1 and a half-life of 14 days for the same concentration of oxamyl in an aqueous solution with a pH of 6.9.

The effect of light on the hydrolysis of oxamyl was also examined. Harvey and Han (1978a) prepared 1 and 1,000 ppm [^{14}C]oxamyl solutions using either distilled or river water. A set of samples was exposed to ultraviolet light continuously for 7 days, while control samples were stored in the dark for 10 days. Aliquots of ultraviolet-exposed samples were analyzed for total radioactivity and composition at 0, 3, and 19 hours, and at 2, 4, and 7 days. Controls were examined only at the end of the 10-day holding period. In all light-exposed samples, decomposition of oxamyl was extensive and rapid. The most dramatic effects were seen in the 1-ppm sample from river water, in which 99% of the radiolabeled oxamyl was hydrolyzed within 48 hours of the initiation

of exposure. At the end of 1 week, 22 to 61% of the parent compound persisted in the other ultraviolet-exposed water samples. The pesticide was converted primarily to the oximino derivative (18 to 51% of the total radioactivity recovered) and its isomer (3% in 1-ppm sample in distilled water; 24 to 36% in all others). A polar fraction N,N-dimethyl(oxamic acid) was present in high concentrations (18 and 23%) in the samples containing 1 ppm only. The level of oxamyl in three of the control samples remained essentially unchanged; however, in river water samples containing 1,000 ppm, 16% of the parent compound was converted to the oximino form after 10 days. Recovery of at least 98% of the original radioactivity was reported for all samples.

In a similar study, 6 gallons of river water spiked with 1 ppm [^{14}C]-oxamyl were left outdoors and exposed to direct sunlight for 6 weeks (Harvey and Han, 1978a). No oxamyl remained at the end of the study. The radiocarbon was present primarily as the oximino derivative (46% of total radioactivity recovered) and its isomer (34%). Polar compounds, including N,N-dimethyloxamic acid and two unknown compounds, comprised the remaining 20% of the carbon label. The authors reported that oxamyl was hydrolyzed completely to the oximino compound by the end of the second day of the study. This compound was gradually converted to its syn-anti-isomer until an apparent equilibrium state was reached. Following this, additional degradation products were formed. Approximately 17% of the total radioactivity was not accounted for during the 6-week experiment. This was presumably lost as $^{14}\text{CO}_2$.

2. Mobility in Soil

Conflicting data exist concerning the mobility of oxamyl in the soil. Harvey and Han (1978a) reported that, under laboratory conditions, oxamyl (levels not specified) was fairly mobile in four soils (muck, loamy sand, and

two types of silt loam). Thin-layer chromatographic (TLC) analysis gave reference (Rf) values (0.53 to 1.00) reflective of a moderately to highly mobile compound (Harvey and Han, 1978a). The mobility of oxamyl increased as the amount of organic matter decreased in the soil; movement was slowest in muck and the most rapid in loamy sand. The K value (Freundlich adsorption constant) for oxamyl was less than 0.1 in the two silt loams and in the loamy sand (adsorption was not measured in muck). Thus, when shaken for 72 hours in a system containing 25 g soil and 30 g water, oxamyl essentially was not adsorbed onto loam or sand.

Field studies indicate that downward movement of oxamyl in soil is not extensive. Analysis of leachate from three types of soil (silt loam, loamy sand, and fine sand) treated with [^{14}C]oxamyl (6 pounds/acre) showed that over a 3- to 5-month period, very little radiocarbon penetrated depths greater than 15 inches below the treated surface (Harvey and Han, 1978a). Only in sandy soil, after 3 months and 23 inches of rain, did more than 1% of the original carbon label reach the 15-inch depth. Most of the radioactivity present was in the form of the oximino metabolite.

In another study, Harvey and Han (1978a) treated the surface of a 1,200 ft² area of silt loam with 5.65 pounds active ingredient (ai)/acre. Over a 30-day period, a total of 8.5 inches of artificial plus natural "rain" fell on the test site. Oxamyl levels were less than or equal to 0.04 ppm at depths up to 30 inches below the ground surface. After treatment, oxamyl concentrations in the 0- to 4-inch soil samples dropped steadily from 2.5 ppm on day 2 to 0.13 ppm on day 30. Throughout the study, no other soil layer contained more than 0.15 ppm oxamyl residue. Oxamyl levels in all soil samples (including surface soil samples) dropped to pretreatment levels within 60 days after exposure to the insecticide.

The results of a 2-year field study conducted by McIntosh et al. (1984) indicated that oxamyl probably does not accumulate in light-textured soils that are heavily irrigated. In this experiment, oxamyl was applied at an approximate rate of 1.0 pound ai/acre/month to sandy desert soils in a southern California lemon grove. Ten pounds/acre were applied during the first year of the study, and 7 pounds/acre were added to the soil in the second year. Five replications of 1/4-acre lots were used. Water-only areas served as controls. Samples were taken at depths of 0 to 4, 4 to 8, and 8 to 12 inches, and at each foot between 1 and 20 feet below the surface of the soil. Analysis of samples obtained between 1 and 35 days posttreatment showed that, under the conditions outlined, oxamyl did not penetrate the soil to depths greater than 5 feet. Oxamyl was rapidly degraded to its oxirino metabolite in these samples. Levels of both compounds were undetectable by 21 days postapplication. Similar results regarding oxamyl penetration and degradation were obtained when a single 10-pound (ai)/acre treatment (10x the normal use rate) of Vydate® was applied to a previously untreated site.

The field study data described above disagree with laboratory data indicating that oxamyl is moderately to highly mobile in soil. Harvey and Han (1978a) concluded that, under practical conditions, rapid degradation of oxamyl precludes its movement in soil despite heavy rainfall.

3. Decomposition in Soil

Degradation and metabolism of oxamyl were examined in three moist soils: sand, sandy loam, and silt loam (Ou and Rao, 1986). Approximately 500 ug [1-¹⁴C]oxamyl were added to 100 g dry soil to give a final pesticide concentration of 5 ug/g. About 59 to 84% of the original carbon label appeared as ¹⁴CO₂ by day 63 postapplication. At this time, most of the remaining

radiolabel was nonextractable (i.e., bound). The exception was the silt loam with a high soil-water tension (33 kPa); in this soil, 24.5% of the original ^{14}C dose appeared as oxamyl, small amounts of N,N-dimethyl-2-(methylthio)acetamide oxime, and polar metabolite. As the soil-water tension increased, degradation of oxamyl decreased. Unchanged parent compound accounted for 28 to 47% and 63 to 79% of the recovered radioactivity at the lowest (10 kPa) and highest (1.5×10^3) tension levels, respectively. Half-lives ($t_{1/2}$) for extractable ^{14}C disappearance ranged from 8 to 50 days; $t_{1/2}$ values for oxamyl disappearance were estimated to be shorter.

Extensive field studies on the decomposition of Vydate® in soil were conducted by Harvey and Han (1978a). In one investigation, three types of soil (silt loam, loamy sand, and fine sand) were treated with [^{14}C]oxamyl at a rate equivalent to 6 pounds ai/acre. All sites were exposed to normal weather conditions and similar amounts of rainfall. Samples were analyzed at 1 week, 1 month, and 3 or 5 months posttreatment. In all three soils, oxamyl was rapidly decomposed; less than 5% of the parent compound remained at the 1-month collection time. After 1 month, volatility losses (presumably as $^{14}\text{CO}_2$) comprised 65.5 to 73.0% of the original ^{14}C application. The oximino derivative of Vydate® and a polar fraction appeared early in the study (at 1 week) and in considerable amounts. However, only trace levels of these radioactive components were detected at the end of the study. Unextracted residue contained 6.3 to 27.0% of the original radioactivity; these levels varied greatly with regard to time and soil type. Five months after spraying, approximately 9% of the original label was extracted from the loamy sand residue and was distributed in the soil as follows: alphanhumus, 32%; soluble humin, 19%; fulvic acid, 13%; beta-humus and insoluble humus, 6% each; hmatomelanic acid, 4%; and a volatile compound lost during analysis, 21%. Detailed analysis of the other soils was

not reported. Leachate water obtained from loamy sand and fine sand contained no radioactivity at 1 week and 1 month and only trace amounts (less than 6% of the original carbon label) at the last sampling time.

Aerated silt loam was treated with [^{14}C]oxamyl (0.98 μCi) at a rate equivalent to 4 pounds/acre (Harvey and Han, 1978a). The experiment was repeated under anaerobic conditions at a level of 6 ppm [^{14}C]oxamyl (7.12 μCi). Both soils were placed in metabolic chambers for 42 days. In the presence of air, 51% of the labeled chemical was converted to $^{14}\text{CO}_2$, 11% appeared as a polar fraction, and 4% remained unchanged. Only a trace amount of the parent compound was present as the oximino form. Approximately 26% of the original radioactivity was incorporated into normal soil organic material. Nearly two-thirds of this residual radioactivity was divided among several soil fractions: fulvic acid, 62%; alpha-humus, 25%; humatomelanic acid, 6%; and beta-humus, 6%. About 7% of the original radioactivity in the aerobic soil samples was not accounted for.

Under anaerobic conditions, decomposition of [^{14}C]oxamyl was almost as rapid and extensive as in the aerobic system in that only 8% of the parent compound remained after 42 days (Harvey and Han, 1978a). However, only 3% of the original radioactivity was converted to $^{14}\text{CO}_2$, and more than 80% appeared as the oximino compound and the polar fraction. Residual levels of radioactivity were low (6%) at the 42-day mark, indicating a delay in both the oxidation of oxamyl to CO_2 and the incorporation of the pesticide into organic matter.

The rate of aerobic and anaerobic decomposition of 6 ppm [^{14}C]oxamyl in loamy sand, fine sand, and silt loam was investigated by Harvey and Han (1978a). Soil samples were analyzed for radioactivity and composition at 0, 7, 14, and 28 days after treatment. Oxamyl concentrations declined steadily in both

aerobic and anaerobic samples; after 28 days, approximately 28% of the parent compound remained in aerated sands, and only 2% persisted in the silt loam deprived of oxygen. Under aerobic conditions, the half-life of oxamyl was 15 days for the fine sandy soil and 11 days for the loamy sand samples. In the absence of oxygen, the half-life of oxamyl was approximately 6 days. On the basis of results from a 2-year field study, McIntosh et al. (1984) reported a half-life of 1 to 4 days for oxamyl when the compound was applied at a rate of 1 pound ai/acre/month to irrigated sandy desert soils. In a field study conducted by Harvey and Han (1978a), a 1,200 ft² area of silt loam was treated with 5.65 pounds ai/acre. Soil samples reaching depths of 30 inches were analyzed on 0, 2, 5, 9, 15, 23, 30, and 60 days after oxamyl application. The half-life of Vydate® under the conditions of this study was 8 days.

4. Metabolic Fate in Plants

The metabolic pathway of [¹⁴C]oxamyl was studied in peanut and tobacco seedlings treated with 2 and 6 pounds ai/acre, respectively (Harvey, 1973). In extracts of young peanuts, peanut hay and seedlings, and mature tobacco, the majority of radioactivity (73 to 100%) was detected in a "polar fraction." At 2 to 6 weeks postspraying, this polar fraction consisted primarily of a glucoside conjugate of a hydrolyzed oximino compound. Demethylation gradually occurred, producing a monomethyl oximino glucoside within 1 to 2 months and an N-demethylated oximino glucoside several months after exposure to the nematocide. Small amounts of oxamyl and its oximino derivative were found in the plant extracts at various stages of harvesting. N,N-dimethyloxamic acid was also detected in tobacco raised in growth chambers. Below are the chemical structures for these compounds. The author suggested that the presence of this compound may represent a minor or alternate metabolic pathway for oxamyl.

COMPOUND	NAME	STRUCTURE
OXAMYL	METHYL N', N'-DIMETHYL-N [(METHYL CARBAMOYL) OXY]-1-THIOXAMMIDATE	
(I)	OXIMINO METABOLITE METHYL N-HYDROXY-N', N'-DIMETHYL-1-THIOXAMMIDATE	
(II)	N, N-DIMETHYLOXAMIC ACID	

In another study, a 1% solution (w/v) of [^{14}C]oxamyl in 0.2% aqueous Tween 20 was spotted on the surface of green tomatoes (Cv. Bonny Best) being grown in a greenhouse (Harvey, 1976). A total of 0.37 mg oxamyl was applied to each tomato. Fruit was allowed to ripen and was harvested in pairs at 7, 11, 14, and 21 days after treatment. At 14 days, the primary residue found on the surface and on the inside of ripe fruit was oxamyl (59% of total radioactivity recovered). Lesser amounts were present as the corresponding oximino compound (13%) and its glucose conjugate (5%). Approximately 4% of the radioactivity was associated with N,N-dimethyl-1-cyanoformamide (UMCF). The remainder of the radiocarbon (19%) was present as a mixture of polar or natural products. Comparable levels of oxamyl and its metabolites were found at 21 days, although a steady decline in oxamyl and an increase in the oximino compound were observed during the 3-week harvesting time.

5. Environmental Toxicity

Technical grade (93.5% pure) or 1% granule oxamyl was dissolved in water at concentrations of 13.5, 18, 24, 32, 42, or 56 ppm (Watanabe, 1975). A 75-ppm solution of the granular formulation was also included in the study. The solutions were transferred to 50-L tanks, and 10 carp (approximately 6.1 cm long and weighing 55 g) were placed in each tank for 48 hours for the purpose of evaluating the acute toxicity of Vydate®. No fish survived the highest concentration level of either type of oxamyl. All animals survived exposure to the

13.5- and 18-ppm solutions, and 10 to 90% of the carp were still alive after swimming in waters containing intermediate concentrations of oxamyl. Up to 50% of the fish were found turning sideways while in the treated water; the bodies of many fish were bent in a U-shape following exposure to the chemical. Fish that died during the study had enlarged gall bladders, hematoceleia, and anemia in the gills. Bent bodies did not return to normal after carp were placed back into fresh water. Forty-eight hour median tolerance limit (TL_m) values were 29 ppm (ai) and 35 ppm (ai) for carp exposed to 1% granule and technical grade oxamyl, respectively, indicating that granule Vydate® is slightly more toxic to carp than is the technical grade. The authors concluded that, at the concentrations investigated, both forms of oxamyl could do considerable harm to fish.

Tadpoles (Rana temporaria) exposed to oxamyl exhibited slowed growth, delayed development, and physical deformities. In this field study (Cooke, 1981), eight cages of 40 tadpoles each were maintained for 60 to 80 days adjacent to sugar beet, barley, and potato fields that had been sprayed with the pesticide (exposure levels not noted). No other chemicals were used during the experiment. In cages kept between fields of barley and potatoes, mortality was high, development and growth were slow, deformities particularly vertical curvature and tail tip, were also found. However, cages kept between barley and sugarbeet, survival was good, development was rapid, and growth was satisfactory. Deformities occurred late in the study showing lateral kinks. Cages kept between sugarbeet and potatoes showed high mortality during the first month but leveled for the rest of the study. Lateral curves and tail tip deformities were also observed. A cage kept in a nature reserve pond served as a control; all parameters measured were normal, except for a few lateral kinks. In a parallel laboratory study, approximately 90% of tadpoles exposed to 100 ppm oxamyl for

1 hour, developed vertical curvature deformities similar to those seen in the field (Cooke, 1981). No tail tip defects developed in the 100-ppm oxamyl-treated tadpoles. The deformities observed under laboratory conditions appeared to be related to abnormal posturing, unlike those found in the field which appear to be of muscular origin. Experimental evidence therefore did not prove conclusively that oxamyl caused the harmful effects observed in field tadpoles. It did indicate however, that oxamyl warrants further consideration.

A significant increase in the mortality rate for bees was observed after oxamyl was sprayed over alfalfa fields (Atkins et al., 1974). Early morning foliar applications of Vydate® (0.5 and 1.0 pound/acre) suppressed bee foraging for at least 4 days. More than 95% of the bees exposed directly to either concentration of the pesticide died within 24 hours; of the bees placed in the field 1 hour after spraying either 0.5 or 1.0 pound/acre, only 29 and 12% died during the next 24 hours, respectively. Approximately 3% of control bees died under similar exposure conditions and times. The overall hazard of Vydate® to bees was moderately high at the 1.0-pound/acre level and moderate for the 0.5-pound/acre concentration.

Under laboratory conditions, oxamyl was toxic to one type of earthworm, the night crawler (Lumbricus terrestris) (Ruppel and Laughlin, 1977). In this study, Vydate® was mixed with dry potting soil at rates equivalent to 0, 2, 4, 8, 16, and 32 pounds ai/acre. Ten active night crawlers were added to each test soil. A relatively high level of the pesticide, 13.06 pounds ai/acre, was required to cause death in 50% of the night crawler population. According to the authors, these data support evidence of high night crawler mortality rates observed in fields sprayed with oxamyl.

The effect of 10 ppm oxamyl on bacterial growth was studied in three types of soil: fine sand, silt loam, and sandy loam (Peeples, 1977). Dilution plate counts were used to determine soil microbial populations at 1, 2, 4, and 8 weeks after treatment. CO₂ evolution was used to measure microbial activity. Oxamyl had no adverse effects on either fungal or bacterial population or on microbial respiration in any of the soil types.

III. TOXICOKINETICS

A. ABSORPTION

Seventy-two hours after two male Charles River-CD rats were given a single oral dose of 1.0 mg (3.74 or 5.6 uCi) [1-¹⁴C]oxamyl, about 55% of the original radioactivity was recovered in the urine (Harvey and Han, 1978b). About 19% of the radiocarbon was found in the hide (skin and hair), the carcass, and various tissues (including plasma but excluding the gastrointestinal tract) at the time of sacrifice (72 hours postdosing). Plasma levels of radioactivity accounted for only 1.55 and 2.13% of the original ¹⁴C dose at 72 hours. These data suggest that at least 74% of the dose is absorbed from the gastrointestinal tract following oral administration.

Chang and Knowles (1979) gave 20 male Swiss-Webster mice a single intraperitoneal (ip) dose of 1.16 mg/kg (0.13 uCi) [1-¹⁴C]oxamyl. Within 96 hours after being injected with the pesticide, mice excreted 88.7 and 7.7% of the radioactive label in the urine and feces, respectively. More than 75% of the original radioactive dose was eliminated during the first 6 hours of the study, with the majority (72.7%) appearing in the urine. At 96 hours after injection, the ¹⁴C concentration in the plasma was only 30.5 ppb; plasma radioactivity levels were not measured at any other time.

B. DISTRIBUTION

Tissue levels of radioactivity were generally low following administration of radiolabeled oxamyl. About 22% of a single oral dose of 1.0 mg [1-¹⁴C]oxamyl (3.74 or 5.6 uCi) retained by two male Charles River-CD rats was distributed among 13 body fractions 3 days after administration (Harvey and Han, 1978b). Approximately 6.98 and 12.55% of the original radiocarbon were recovered in the

hide (skin and hair), 6.34 and 4.18% were retained in the carcass, 4.76 and 1.32% were found in the gastrointestinal tract, and 1.55 and 2.13% were present in the blood. The liver of one animal contained 1.58% of the original radioactivity, while the hepatic ^{14}C level in the second rat was only 0.20%. Other tissues contained no more than 0.36% of the original ^{14}C label (Harvey and Han, 1978b).

In the study conducted by Chang and Knowles (1979), radiocarbon residues in tissues of 20 Swiss-Webster male mice given single intraperitoneal injections of 1.16 mg/kg (0.13 μCi) [^{14}C] oxamyl were very low. Residue levels ranged from 11.0 ppb in the testes to 37.0 ppb in the liver 96 hours after dosing.

C. METABOLISM

Oxamyl is metabolized extensively in rats and mice. Urine and feces collected from two male Charles River-CD rats given a single oral dose of 1.0 mg [^{14}C]oxamyl were analyzed 72 hours after dosing; more than 70% of the recovered radioactivity appeared as conjugates of the oximino metabolite of oxamyl (methyl N-hydroxy-N',N'-dimethyl-1-thiooxamimidate, DMT0; Fig. III-1-I) and N,N-dimethyloxamic acid (DMOA; Fig. III-1-III), and as the monomethyl derivatives methyl N-hydroxy-N'-methyl-1-thiooxamimidate (MT0; Fig. III-1-II) and N-methyloxamic acid (MOA). The percent distribution of these four metabolites was roughly equivalent in both urine and feces, although the urine contained approximately 55% of the original radioactivity and feces contained about 15%. No oxamyl or other organosoluble metabolites, including N,N-dimethyl-1-cyanoformamide (DMCF), were found in urine, feces, or tissues. Approximately 43 and 51% of the radioactivity recovered, respectively, in the plasma and hide of rats was incorporated into various amino acids (Harvey and Han, 1978b). In the

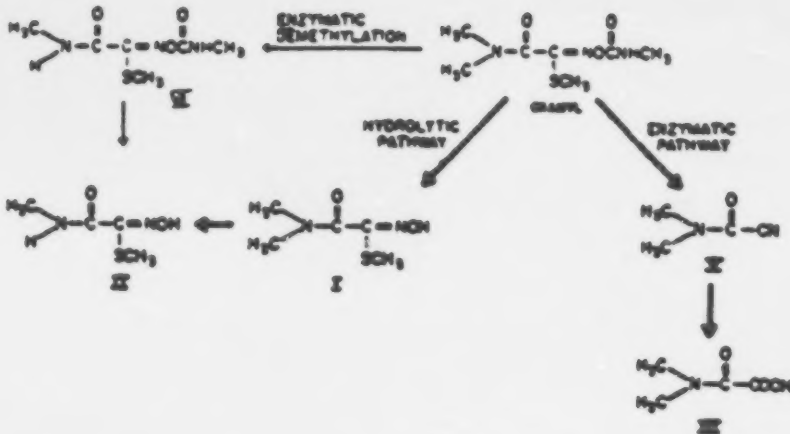


Figure III-1. In vitro metabolism of oxamyl by rat liver microsomes.

- I: DMT0
II: Methyl N-hydroxy-N'-methyl-1-thiooxamimidate (MT0)
III: DMOA
V: DMCF
VI: Methyl N'-methyl-N-[(methylcarbamoyl)oxy]-1-thio-oxamimidate (UMO).

SOURCE: Adapted from Harvey and Han (1978b).

skin and hair, ^{14}C was associated primarily with glycine, tryptophan, leucine, phenylalanine, and aspartic acid; leucine, glutamic acid, lysine, arginine, and tryptophan contained the greatest proportions of radiocarbon recovered in the blood.

The metabolic profile of urine collected from 20 male Swiss-Webster mice given single ip injections of 1.16 mg/kg [^{14}C]oxamyl was similar to that in rats (Chang and Knowles, 1979). The major urinary metabolite was DMTU, which accounted for an average of 43.5% of the radioactivity excreted by the animals during the 96-hour postdose collection period. Urinary DMOA ranged from 8.9 to 27.2% of the recovered radioactivity, with the highest concentrations appearing early in the study. MOA levels increased steadily from 2.3 to 9.9% during the 96 hours after dosing, and MTU levels, which peaked at 15% after 2 days, dropped to 6.9% during the last interval of the study (72 to 96 hours after dosing). In contrast to rats, mice excreted both unchanged oxamyl and DMCF, which comprised up to 18.3 and 3.0% of the total radioactivity recovered in the urine, respectively. Six unknown compounds were also excreted by mice. Results from this study indicate that demethylation of oxamyl and its metabolites occurs with time. The data also suggest that, although the metabolism of oxamyl varies slightly between rats and mice, oxamyl degradation in these two species is generally similar to that in plants and in the environment (see Chapter II, Physical and Chemical Properties).

In another experiment by Harvey and Han (1978b), one rat dosed with 1.1 mg (10.7 μCi) [^{14}C]DMCF (rather than oxamyl) excreted conjugates of DMOA and MOA (15 and 7%, respectively, of the total radioactivity) in the urine over a 72-hour period after dosing. An additional 27% of the radiocarbon recovered in the urine was associated with amino acids. The authors postulated that the

remaining ^{14}C was probably incorporated into other natural constituents. Tissues, carcass, and blood from the $[1-^{14}\text{C}]\text{DMCF}$ -treated rat contained very low levels of radioactivity; 23 to 89% of the ^{14}C residues from these fractions appeared as amino acids. The absence of DMCF in rat urine and the similarities in metabolites from oxamyl- and DMCF-treated rats suggests that DMCF is only an intermediate in the metabolism of oxamyl in the rat.

In vitro data support in vivo metabolism studies in rats and mice. In a study conducted by Harvey and Han (1978b), three levels of $[1-^{14}\text{C}]\text{oxamyl}$ (0.3, 1.0, and 2.0 mg) were incubated for 2 hours with microsomal and/or soluble (cytosolic) fractions obtained from the livers of Charles River-CD rats. A control system containing 1.0 mg of $[1-^{14}\text{C}]\text{oxamyl}$ but no hepatic microsomal fraction accompanied each test system. In addition to oxamyl, DMT0, DMCF, and DMOA were present in substantial amounts at the end of the 2-hour reaction period. These four compounds comprised 93.5 to 96.8% of the total radioactivity. Small amounts of the monomethyl derivatives of oxamyl and its oximino compound (DMTU) were also present in the incubation medium. The control medium contained only DMT0 in approximately the same concentration as in the test samples, suggesting that hydrolysis of oxamyl is independent of the liver microsomal fraction.

After a 2-hour in vitro incubation period with $[1-^{14}\text{C}]\text{oxamyl}$ (200,000 dpm) and mouse liver subcellular fractions, the primary metabolite formed was DMT0 (12.5 to 24.0% of the total recovered radiocarbon) (Chang and Knowles, 1979). Oxamyl as parent compound represented approximately 70 to 80% of the total radioactivity. DMCF, DMOA, MOA, methyl N'-methyl-N-[(methylcarbomoyl)oxy]-1-thioxamimidate (DMU), and several unknown compounds were also present, but in very low concentrations.

On the basis of in vivo and supporting in vitro data, Harvey and Han (1978b) postulated that oxamyl metabolism occurs by two major pathways: by hydrolysis to DMTU and by enzymatic conversion via DMCF to DMOA. Superimposed on these two pathways is another slower enzymatic process that results in partial demethylation of the dimethyl carbamoyl group. The proposed in vitro metabolism of oxamyl by rat liver microsome (Harvey and Han, 1978b) appears in Figure III-1. The authors did not comment on the metabolic incorporation of ^{14}C into the various amino acids, nor did they report the position(s) of the carbon label associated with radiolabeled amino acids.

Oxamyl metabolism in vitro and in vivo is very similar. The two pathways share three major products: DMTU, DMOA, and MTU. Rats and mice also excrete MOA following either oral or ip dosing. Demethylation has been demonstrated in both in vivo and in vitro studies. Differences in oxamyl metabolism become evident when comparing species. DMCF is considered a metabolic intermediate only in rats, but the compound is actually excreted in the urine of mice. Unchanged oxamyl is completely metabolized by orally dosed rats and by microsomes isolated from rat hepatocytes, whereas the urine of ip-dosed mice contained up to 18.3% of the unchanged parent compound (Harvey and Han, 1978b).

D. ELIMINATION

Oxamyl is rapidly eliminated following ingestion in rats and ip dosing in mice. In both species, elimination occurs primarily via the urine. Two Charles River-CD rats treated with a single oral dose (1.0 mg) of $[1-^{14}\text{C}]$ oxamyl excreted an average of 55 and 15% of the original radiocarbon in the urine and feces, respectively, during the 72-hour period that followed dosing (Harvey and Han, 198b). Little radioactivity (less than 0.3%) appeared in expired air of dosed

rats. In a study with 20 male Swiss-Webster mice, 88 and 7% of a 1.16-mg/kg ip-dose of [^{14}C]oxamyl appeared in the urine and feces, respectively, by 72 hours; more than 75% of the dose was eliminated in the urine (72.7%) and feces (3.0%) during the initial 6 hours after administration (Chang and Knowles, 1979).

E. BIOACCUMULATION AND RETENTION

No information on the bioaccumulation or retention of oxamyl following repeated dosing was found in the available literature. Due to the rapid excretion and metabolism of the compound, and low tissue levels in 20 ip-dosed mice, significant accumulation and retention of the pesticide are not expected. However, the presence (at 72 hours postadministration) of approximately 19% of an oral dose of 1.0 mg [1- ^{14}C]oxamyl in each of the bodies of two rats given the chemical suggests that oxamyl or its metabolites may accumulate in or be retained by various body fractions, such as the skin, hair, carcass, liver, and blood. Incorporation of ^{14}C from the tagged parent compound into natural constituents (e.g., amino acids) also points to retention of oxamyl by the body.

F. SUMMARY

Oxamyl is rapidly absorbed, metabolized, and eliminated. In orally treated rats, more than half (54.8%) of an oxamyl dose was eliminated in the urine and about 15% in the feces within 3 days after ingestion. Mice excreted approximately 87% of an ip dose of oxamyl in the urine and 7.2% in the feces by 4 days postadministration.

Due to rapid elimination of a large proportion of administered [^{14}C]oxamyl doses, individual tissue levels of radioactivity remain low in ip-dosed mice. Oxamyl, or its metabolites, did not accumulate to any appreciable amount in any

tissue in that species, although in two orally dosed rats, 7 to 12.5% of the original ^{14}C was recovered in the hide (skin and hair) 3 days after dosing, and a total of 19% was retained by the whole body.

Oxamyl was extensively metabolized following oral administration to rats and ip administration to mice. The primary urinary metabolites excreted by both species were DMTU, DMOA, MOA, and MTU. Unlike rats, mice excreted the unchanged parent compound as well as DMCF. In vitro studies demonstrate that oxamyl is metabolized by hepatic microsomes via two major pathways; the first involves hydrolysis to UMTU, and the second involves enzymatic conversion via DMCF to DMOA. A minor enzymatic process, which results in partial demethylation of oxamyl and its metabolites, was also noted.

Based on the above findings, accumulation and retention of oxamyl in the body is not expected, although radiolabel from the oxamyl moiety [^{14}C] has been found in amino acids.

IV. HUMAN EXPOSURE

To be provided by Science and Technology Branch, Office of Drinking Water.

V. HEALTH EFFECTS IN ANIMALS

A. SHORT-TERM EXPOSURE

1. Lethality

Oxamyl has been shown to be extremely toxic when administered orally to laboratory animals. Kennedy (1986a) reported acute oral LD₅₀ values of 2.5 to 3.1 mg/kg for fasted rats, 2.3 to 3.3 mg/kg for mice, and 7.0 mg/kg for guinea pigs. Typical signs of cholinesterase inhibition such as tremors, salivation, and lacrimation were noted immediately after dosing (Kennedy, 1986a).

Oxamyl is also extremely toxic after intraperitoneal injection. An LD₅₀ in rats of 4.0 mg/kg was reported by Kennedy (1986a). Single intraperitoneal injections of oxamyl in saline resulted in mortality within 2 hours in mice given doses of 2.3 mg/kg or greater and in guinea pigs given doses of 5.1 mg/kg or greater (Kennedy, 1986a). Oxamyl is less toxic via the dermal route; LD₅₀ values of 750 and >1,200 mg/kg were reported in rabbits and rats, respectively. From these results, oxamyl appears to be only partially absorbed through the skin. However, clinical signs of cholinesterase inhibition were noted in animals given dermal doses of oxamyl (Kennedy, 1986a).

The 1-hour LC₅₀ for rats exposed to oxamyl via inhalation (head-only exposure) were 0.17 mg/L for males and 0.12 mg/L for females. The 4-hour LC₅₀ was 0.064 mg/L for male rats. Clinical signs noted during exposure included exophthalmos, salivation, lacrimation, and gasping (Kennedy, 1986a).

A summary of the LD₅₀ and LC₅₀ values of oxamyl is presented in Table V-1.

Table V-1. Summary of Acute Toxicity Values in Laboratory Animals
After Exposure to Oxamyl

Species (Sex)	Exposure route	Acute toxicity value	Reference
Rat (M)	oral	LD ₅₀ : 3.1 mg/kg	Kennedy (1986a)
Rat (F)	oral	LD ₅₀ : 2.5 mg/kg	--
Rat (M)	oral	LD ₅₀ : 4.0 mg/kg	Reinhart (1971)
Rat (F)	oral	LD ₅₀ : 2.8 mg/kg	--
Mouse (M)	oral	LD ₅₀ : 3.3 mg/kg	Kennedy (1986a)
Mouse (F)	oral	LD ₅₀ : 2.3 mg/kg	--
Guinea pig (M)	oral	LD ₅₀ : 7.0 mg/kg	Kennedy (1986a)
Rat	ip	LD ₅₀ : 4.0 mg/kg	Kennedy (1986a)
Rat	dermal	LD ₅₀ : >1200 mg/kg	Kennedy (1986a)
Rabbit	dermal	LD ₅₀ : 740 mg/kg	Kennedy (1986a)
Rat (M)	inhalation	LC ₅₀ : 0.17 mg/L (1-hr)	Kennedy (1986a)
Rat (F)	inhalation	LC ₅₀ : 0.12 mg/L (1-hr)	--
Rat (M)	inhalation	LC ₅₀ : 0.064 mg/L (4-hr)	Kennedy (1986a)

2. Other Effects

The ability of oxamyl to inhibit serum cholinesterase activity was studied in 10 rats given a single oral dose of 4.86 mg/kg oxamyl approximately 90% of LD₅₀. This dose resulted in an approximately 40% decrease in serum cholinesterase activity (decreased from a mean pretreatment value of 4.3 to a posttreatment value of 2.6 μ mol substrate hydrolyzed/mL/5 min) 5 minutes after exposure and a 60% decrease (1.8 ± 0.7 μ mol substrate hydrolyzed/mL/5 min) 4 hours after administration. Activity returned to normal level of 5.7 24 hours after administration (Kennedy, 1986a). Little or no cholinesterase inhibition was observed when atropine sulfate (50 mg/kg) was administered by ip injection immediately after oxamyl administration. No mortality occurred when atropine was injected after a dose of oxamyl that normally would kill 50% of the rats; however, fasciculations were noted in rats receiving the oxamyl/atropine combination (Kennedy, 1986a).

Rats (six males) given repeated oral doses of 2.4 mg/kg of oxamyl 5 days/week for 2 weeks exhibited mild fasciculations that lasted 2 to 4 hours during the first week and 1 to 2 hours during the second week. Slight decreases in body weight were noted. The author stated that rats exhibited salivation and slight pallor after the first two doses, but no clinical signs were noted thereafter (Kennedy, 1986a). Hence, it appears that the rats developed a slight tolerance to oxamyl after 1 week of oral dosing.

Oxamyl appears to be less toxic to dogs after oral administration. Male beagles were given single oral doses of 5, 10, 15, or 30 mg/kg and observed for 21 days. All the oxamyl-treated dogs exhibited clinical signs of cholinesterase inhibition, and one dog given 30 mg/kg died (Kennedy 1986a).

Repeated application of 50 or 100 mg/kg of oxamyl in a dimethylformamide (DMF) vehicle to the abraded or intact skin of groups of five male and five female rabbits, 6 hours/day for 15 days, resulted in fasciculations, irregular breathing, reduced coordination, and salivation after each dose. These effects lasted approximately 4 hours (Kennedy, 1986a). No effects were reportedly noted in controls exposed to DMF only. In a similar study, minimal effects were noted in groups of six male rabbits after application of 50 or 100 mg/kg oxamyl in an aqueous methanol vehicle to intact or abraded skin. Apparently, the dimethylformamide vehicle increased the absorption of oxamyl through the skin, resulting in greater toxicity.

Minimal effects were noted after instillation of oxamyl (10 mg) into the eyes of rabbits. Slight constriction of the pupils, minimal congestion of the iris, and mild redness and swelling of the conjunctiva were reported (Kennedy 1986a). Eyes were essentially normal by 24 hours postadministration. Kennedy (1986a) reported that one of four rabbits exhibited reduced muscular coordination in the hind limbs 20 minutes postdose; therefore, it appears that some absorption of oxamyl occurred after ocular exposure.

B. LONG-TERM EXPOSURE

1. Subchronic Toxicity

Haskell Laboratory conducted a study in which groups of 10 weanling Crl:CD rats of each sex were fed diets containing 0, 50, 100, or 150 ppm of oxamyl (>95% purity) for 90 days. These were comparable to dose levels of approximately 0, 2.5, 5.0, and 7.5 mg/kg/day. Initially, for the first 4 days of feeding, the high-dose group actually received 500 ppm of oxamyl in the

diet. This dose caused immediate, excessive weight loss, as well as fasciculation, ruffled fur, and mild diarrhea in male rats. The males and females fed the high dosage were then placed on control diets for 3 days. From day 8 to termination of the study, the high-dose group received 150 ppm in the diet. The only obvious sign of toxicity due to oxamyl administration was in body weight. Body weights were significantly lower ($p < 0.05$) than controls in males fed 100 or 150 ppm of oxamyl from days 28 to 91 of the study. In females receiving 100- and 150-ppm levels, body weight gains were lower, but decreases were only sporadically significant compared to controls. No clinical signs of toxicity were noted during the study except for few unclear and inconsistent occurrences of proteinuria and occult blood appeared to be higher in the groups fed the 100- and 150-ppm dietary levels compared to controls. The toxicological significance of this is unclear. Pathologic examination revealed no abnormalities (Kennedy, 1986b).

In a separate 90-day feeding study, groups of four young adult beagles of each sex were given 0, 50, 100, or 150 ppm of oxamyl ($\geq 95\%$ purity) in the diet (equivalent to dose levels of approximately 0, 1.3, 2.5, and 3.8 mg/kg/day, respectively). No compound-related changes in body weight gain, food consumption, clinical signs, hematology, clinical chemistry, or pathologic findings were noted in both the control and compound-treated dogs. Only one control male dog lost 1.1 kg weight; the rest maintained or gained weight. The author reported infrequent, sporadic incidences of bloody mucoid diarrhea, eye discharge, inflammation, dehydration, thinning hair on chest, and cysts in dogs receiving oxamyl, but these were not considered to be related to oxamyl administration (Kennedy, 1986b).

2. Chronic Toxicity

Three long-term feeding studies with oxamyl have been reported (Kennedy, 1986b). In the first study conducted at Haskell Laboratory, groups of 36 weanling Crl:CD rats of each sex were given 0, 50, 100, or 150 ppm of oxamyl (95% purity) in the diet for 2 years, corresponding to doses of approximately 0, 2.5, 5.0, and 7.5 mg/kg/day. An additional control group of 36 male and 36 female rats was fed a diet containing 0 ppm oxamyl. A three-generation reproduction study was conducted simultaneously using 16 male and 16 female rats from each test group and one control group. Animals were mated after 12 weeks of exposure to test diets. Further details on the reproduction study will be given in the following section. Cholinesterase activity in the whole blood (μmol acetylthiocholine hydrolyzed in 5 min/mL blood) from control animals, and animals fed 100 or 150 ppm was measured periodically during the study. Significant decreases ($p \leq 0.05$) in cholinesterase activity were noted in females receiving the high dose (approximately 20% inhibition) after 4 days and in males receiving the high dose (approximately 33% inhibition) after 8 days on study. However, after 1 month, cholinesterase activity returned to normal and remained within normal range throughout the remaining 2 years of exposure to 150 ppm of oxamyl. Body weights were decreased in a dose-related manner with significant reductions ($p \leq 0.05$) noted in the groups fed 100 and 150 ppm (males and females) compared to controls throughout the study (Table V-2). Females fed 50 ppm oxamyl showed no change in body weight throughout the study except at 24 months when mean body weight was significantly reduced ($P < 0.05$). Slight decreases in food consumption of the group fed 150 ppm compared to the control group were reported. No clinical signs of toxicity attributable to oxamyl administration were noted, and mortality rates were comparable between control and test groups. Slight decreases in absolute organ weights (liver, spleen, kidneys) were noted

Table V-2. Mean Body Weights of Rats Fed Oxamyl for 2 Years

Months on study	Dietary level (ppm)				
	0	0	50	100	150
Males (weight in grams)					
0	140	142	142	140	139
1	343	341	326	304*	282*
3	503	507	492	474*	442*
6	614	601	584	565	511*
12	744	738	725	697*	626*
18	762	778	782	754	768*
24	799	806	744	750	675*
Females (weight in grams)					
0	118	119	121	119	119
1	208	210	206	186*	183*
3	287	293	254	252*	248*
6	343	348	338	290*	282*
12	446	469	440	345*	328*
18	569	562	555	432*	389*
24	640	635	588*	460*	415*

*Significantly different from control value ($p \leq 0.05$).

SOURCE: Adapted from Kennedy (1986b).

in males and females fed 100 or 150 ppm of oxamyl, but these changes were not statistically significant. Organ-to-body weight ratios were comparable between controls and test groups. Therefore, the organ weight changes were attributed to decreased body weight. Histopathologic examination revealed no compound-related abnormalities. Tumor incidences were comparable between controls and test groups. The NOAEL for this study was identified as 50 ppm (2.5 mg/kg/day) of oxamyl.

A second chronic study was conducted at WIL Research Laboratory (1981). Groups of 80 male and 80 female CD-1 mice were fed 0, 25, 50, or 75 ppm of oxamyl (97.1% purity) in the diet for 2 years. These dietary levels were equivalent to mean doses of 0, 3.75, 7.5, and 11.25 mg/kg/day. Initially, the high-dosage group received 100 ppm of oxamyl. However, excessive mortality occurred at this dietary level (10 males and 8 females in the first month on study); therefore, the high dosage was reduced to 75 ppm at week 6. The only clinical signs attributable to oxamyl administration were noted in animals dying prior to terminal sacrifice. These included emaciation, lethargy, and moribundity. Slight, sporadically significant decreases ($p \leq 0.05$) in body weights were noted in animals from the groups fed 50 or 75 ppm, particularly in the first 6 months of the study. Several hematologic parameters (hemoglobin, hematocrit, and red cell count) were significantly reduced ($p < 0.01$) in the males fed the high dose compared with controls at week 4. These parameters were within normal ranges from week 13 to study termination. Histopathological examination revealed no lesions attributable to oxamyl administration. Chronic nephritis was noted in a number of animals at terminal sacrifice. However, increased incidences were noted in control animals compared to other groups; control males had an incidence of 52% compared with 23, 20, and 13% for the males fed oxamyl at 25, 50, and 75 ppm, respectively. The incidence of

chronic nephritis in control females was 15% compared with 6, 10, and 3% for females fed oxamyl at 25, 50, and 75 ppm, respectively. Tumor incidences were similar for control and test groups (WIL, 1981; Kennedy, 1986b). The NOAEL for this study was 25 ppm (3.75 mg/kg/day).

Kennedy (1986b) also reported the results of a 2-year feeding study in beagle dogs conducted at Haskell Laboratory. Groups of four dogs of each sex were fed diets containing 0, 50, 100, or 150 ppm of oxamyl for 2 years. These dietary levels were equivalent to approximately 0, 1.3, 2.5, and 3.8 mg/kg/day, respectively. No mortalities occurred during the study. Body weights, food consumption, clinical observations, and hematological and urinalysis parameters were comparable between controls and test groups. Serum alkaline phosphatase activity and cholesterol levels were increased (2 standard deviations above pretest values for all groups) in animals fed 150 ppm compared to all other dose groups including controls (significance was not reported). Histopathologic findings were observed with equal frequency in all groups including controls. There were no increases in incidences of lesions that could be attributed to the ingestion of oxamyl.

C. TERATOGENIC/REPRODUCTIVE EFFECTS

Kennedy (1986b) reported the results of a teratogenicity study in rats conducted by Haskell Laboratory (1971). Five groups of at least 22 timed-pregnant Crl:CD rats were fed diets containing 0, 50, 100, 150, or 300 ppm of oxamyl on days 6 to 15 of gestation, corresponding to doses of 0, 2.5, 5.0, 7.5, and 15 mg/kg/day, respectively. Although not significantly different, body weights of dams fed oxamyl were decreased in a dose-related manner. An approximately 42% decrease in body weight gain was observed during the study in dams fed 300 ppm of oxamyl compared to controls (Table V-3). A corresponding

Table V-3. Mean Maternal Body Weights of Rats Fed Oxamyl During Gestation

Dietary level (ppm)	Mean body weights (g) during gestation days:		
	6	16	20
0	218 ^a	295	362
50	221	289	358
100	218	264	334
150	214	250	324
300	216	228	300

^a Standard deviations were not reported.

SOURCE: Adapted from Haskell Laboratory (1971).

dose-related decrease in food consumption was observed in dams fed oxamyl. No significant differences were noted in number of implantation sites, live fetuses, or resorptions between test groups and controls (Table V-4). Fetal growth, as measured by body weight and crown-to-rump length, was comparable between control and test groups. The incidences and types of soft tissue and skeletal abnormalities were similar in fetuses from dams fed either control or test diets. In this study, oxamyl was not teratogenic in rats.

In a teratogenicity study with rabbits conducted at Hazleton Laboratories (Snyder, 1980; Kennedy, 1986b), groups of 17 artificially inseminated New Zealand White rabbits were given oral doses of 0, 1, 2, or 4 mg/kg/day of oxamyl (97.1% purity) on days 6 to 19 of gestation. Two rabbits died during the study (one each from the control and 300-ppm groups), but these deaths were probably due to technical errors in dosing. Significant decreases ($p < 0.05$) in body weight gain were noted in dams administered 2 and 4 mg/kg/day during the treatment period (days 6 to 19 of gestation) compared to controls (Table V-5). There was a corresponding decrease in food consumption in the rabbits administered 2 and 4 mg/kg/day during the treatment period. After the dosing regimen ended, however, the rabbits appeared to recover: body weight gains of dams administered 2 and 4 mg/kg/day exceeded those of controls during days 19 to 29 of gestation, and body weight gains for the entire study were comparable between controls and all test groups. Mean number of implantations and live fetuses, and sex ratios were comparable between controls and all test groups. Both Snyder and Kennedy reported a slight increase (not significant) in the incidence of resorptions in the group administered 4 mg/kg/day (mean incidence of resorptions was 10.4 and 24.8 for control and high-dose groups, respectively), indicating a slight embryotoxic effect. Fetal body weights and crown-to-rump measurements were similar in control and test groups. Slight increases (not

Table V-4. Effects of Dietary Administration of Oxamyl on Pregnant Rats and Their Offspring

Parameter	Dietary level (ppm)				
	0	50	100	150	300
Females pregnant/ female on study	22/26	26/27	25/28	26/28	23/28
No. of implantations/ litter	10.6 $\pm$ 1.8	10.8 $\pm$ 2.2	11.3 $\pm$ 1.9	10.3 $\pm$ 2.5	10.8 $\pm$ 2.4
Live fetuses/litter	10.0 $\pm$ 2.2	10.2 $\pm$ 2.1	10.8 $\pm$ 2.0	9.8 $\pm$ 2.5	10.1 $\pm$ 2.6
Litters with resorptions (%)	9 (41)	11 (42)	9 (36)	9 (35)	10 (44)
Total number of resorptions (%)	13 (6)	17 (6)	12 (4)	14 (5)	16 (6)
Fetal body weight (g)	3.8 $\pm$ 0.4	4.0 $\pm$ 0.3	3.9 $\pm$ 0.3	4.0 $\pm$ 0.4	3.8 $\pm$ 0.4

SOURCE: Adapted from Kennedy (1986b).

Table V-5. Mean Maternal Body Weight Gains in Rabbits Given Oral Doses of Oxamyl During Gestation

Dose level (mg/kg/day)	Body weight gain (g) on gestation day:			
	0-6	6-19	19-29	0-29
0	58.0	169.5	138.4	365.9
1	66.0	154.4	144.1	368.7
2	59.7	65.2*	157.1	282.0
4	113.1	55.6*	218.6	387.3

*Significantly different from controls at $p < 0.05$.

SOURCE: Adapted from Snyder (1980).

significant) were observed in the number of visceral and skeletal abnormalities (variants and anomalies) in litters from dams administered 1 mg/kg/day compared to other groups including controls (Table V-6). These increased incidences did not occur in a dose-related manner and were not statistically significant. Therefore, they were considered to be incidental occurrences. The author concluded that oxamyl was not teratogenic in rabbits under the conditions of this study.

A one-generation reproduction study was conducted by Haskell Laboratory (Kennedy, 1986b). Groups of six Cr1:CD rats of each sex were fed diets containing oxamyl at levels of 0, 50, 100, or 150 ppm (equivalent to doses of 0, 2.5, 5.0, and 7.5 mg/kg/day) continuously for 91 to 95 days and mated to produce two litters (F_{1a} and F_{1b}). This study was run concurrently with a 90-day feeding study (see Section V.B.1.). Body weights were significantly decreased ($p \leq 0.05$) in parental males fed 100 or 150 ppm starting 28 days after initiation of the study. Decreases were also observed in parental females from the groups fed 100 and 150 ppm, but significant changes were sporadic. Fertility did not appear to be affected by ingestion of oxamyl. The number of F_{1a} pups delivered to dams from the 100- and 150-ppm groups, and the number of F_{1b} pups delivered to dams fed 150 ppm of oxamyl, were slightly decreased compared to controls. Survival of pups was not affected during lactation. Significant decreases ($p \leq 0.05$) were observed in the body weights of weanlings from both F_{1a} and F_{1b} litters in the groups fed 50, 100, and 150 ppm compared to controls.

A subsequent three-generation reproduction study in rats was conducted concurrently with a 2-year feeding study (Section V.B.2.). After approximately 12 weeks of ingestion of oxamyl at dietary levels of 0, 50, 100, or 150 ppm, 16 male and 16 female Cr1:CD rats from each group were paired (F₀ parental

Table V-6. Summary of Visceral and Skeletal Findings in Fetuses of Rabbits Given Oxamyl During Gestation^a

Observation	Dosage levels (mg/kg/day)			
	0	1	2	4
No. examined	113	90	89	75
Visceral Examination				
<u>Variants:</u>				
Intermediate lobe of lung absent	0	3	1	0
Very small stomach	0	2 ^{bc}	0	0
Slightly dilated renal pelvis	1	2	1	0
<u>Anomalities:</u>				
Hydrocephaly	0	2 ^{bc}	0	0
Cleft palate	0	1 ^c	0	0
Ectopic kidney	0	1	0	0
Skeletal Examination				
<u>Variants:</u>				
Angulated hyoid wing	3	3	1	0
Fused sternbrae	0	2	1	0
Fused ribs	0	2	1	0

^aNumbers represent the number of pups affected in group.

^{bc}The same superscripts indicate the same pup.

SOURCE: Adapted from Synder (1980).

generation) to produce two litters (F_{1a} and F_{1b} generations). The F_{1b} and F_{2b} generations were mated at approximately 110 days of age to produce F₂ and F₃ generations (two litters each), respectively. Reproductive indices such as fertility index, gestation length, pup viability, and lactation index were comparable between control and test groups for all generations. Litter size and mean body weights of weanlings from dams ingesting the 100- or 150-ppm levels of oxamyl were significantly decreased ($p < 0.05$) in the majority of generations compared to controls (Table V-7). Histopathological examination of animals from each generation (parents and offspring) revealed no abnormalities attributable to oxamyl ingestion (Kennedy, 1986b).

D. MUTAGENICITY

Limited information was available in the literature on the mutagenicity of oxamyl.

1. Gene Mutation Assays (Category 1)

a. Gene mutation in prokaryotes

Moriya et al. (1983) reported the evaluation of oxamyl in the mammalian/microsome reverse mutation assay (Ames test). Salmonella typhimurium, strains TA100, TA98, TA1535, TA1537, and TA1538, and Escherichia coli, strain WP2 hcr, were exposed to concentrations of up to 5,000 ug/plate of oxamyl with or without activation (rat liver S9 mix). Results were negative, indicating that oxamyl is not mutagenic to S. typhimurium or E. coli. Negative results were also reported by Shirasu et al. (1976) following a reverse mutation assay conducted in S. typhimurium strains TA1535, TA1537, TA1538, TA98, and TA100, and E. coli strain WP2 hcr. Concentrations of 10 to 1,000 ug/plate of oxamyl

Table V-7. Effects of Oxamyl Ingestion on Litter Size and Body Weights of Weanlings In Three Generations of Rats

Dietary level (ppm)	Generation	Mean litter size ^a	Mean weanling body weight (g)
0	F _{1a}	12.3	53
50		10.9	52
100		10.2*	44*
150		10.4	39*
0	F _{1b}	13.6	57
50		12.3	55
100		11.3*	47*
150		11.1*	42*
0	F _{2a}	11.9	53
50		12.3	49
100		10.6	41*
150		10.4*	36*
0	F _{2b}	12.9	57
50		12.5	52
100		11.0*	42*
150		11.0*	37*
0	F _{3a}	12.4	52
50		12.2	48
100		10.2*	43*
150		9.9*	37*
0	F _{3b}	12.6	52
50		13.1	50
100		12.2	39*
150		10.3*	37*

^aNumber of pups per litter.

*Significantly different from control value ($p \leq 0.05$).

SOURCE: Adapted from Kennedy (1986b).

in the absence or presence of an activation system (rat liver S9 mix) were not mutagenic.

b. In vitro gene mutations

No mutagenic response was obtained in a host-mediated assay with S. typhimurium, strain G 46 hys, after oral administration of oxamyl at total doses of 2 or 4 mg/kg to male ICR mice (two equal doses were administered over a 24-hour period) (Shirasu et al., 1976).

The mutagenic potential of oxamyl was tested in Chinese hamster V79 target cells with or without activation (irradiated Syrian hamster fetal cells). Treatment with oxamyl (concentrations not specified) for 72 hours, with or without activation, had no significant effect on mutagenic frequency (Wojciechowski and Kaur, 1980).

2. Chromosome Aberration Assays (Category 2)

No chromosome aberration studies with oxamyl were found in the available literature.

3. Other Mutagenic Mechanisms (Category 3)

The evaluation of the effect of oxamyl (94% purity) on DNA-damage/repair capability was evaluated using Bacillus subtilis strains H-17 Rec⁺ and M-45 Rec⁻. Concentrations of 20 to 2,000 ug/disk did not preferentially inhibit the repair-deficient strain (M-45 Rec⁻) compared to the repair-competent strain (H-17 Rec⁺) (Shirasu et al., 1976).

E. CARCINOGENICITY

Two chronic feeding studies in rodents have been conducted and were described earlier (see Section V.B.2.) In the feeding study conducted with rats at Haskell Laboratory (Sherman et al., 1972), groups of 36 male and 36 female Cr1:CD rats were fed oxamyl at 0, 50, 100, or 150 ppm for 2 years (equivalent to mean doses of 0, 2.5, 5.0, and 7.5 mg/kg/day, respectively. Significant decreases in body weight were observed in both males and females fed 100 or 150 ppm compared to controls. A summary of the histopathological findings is presented in Table V-8. The incidence of mammary tumors was 67% in control females and 33% in females fed 150 ppm; no mammary tumors occurred in males. Pituitary tumors occurred in incidences of 23 (one of the control groups) to 33% in males fed 150 ppm and 57 (one of the control groups) to 37% in treated females. After reanalysis of the statistics, there appeared to be a significant increase ($p < 0.05$) in the incidence of liver microgranulomas in both males and females fed 150 ppm compared to controls. This lesion is characterized by a granular change in the liver and considered nonneoplastic. Tumor incidences were comparable between the control group and the high-dose group. In this study, oxamyl did not induce a carcinogenic response in rats (Kennedy, 1986b). It should be noted, however, that several deficiencies existed in this study. Adequate numbers of animals were not tested or examined histopathologically (36/sex/group). Possible target organs such as the liver or reproductive organs were apparently not histologically examined in all dose groups. In addition, tumors observed, i.e., those found in mammary and pituitary tissue, were not adequately described in the report.

In the second feeding study, groups of 80 CD-1 mice of each sex were fed diets containing oxamyl at 0, 25, 50, or 75 ppm for 2 years, corresponding to mean dosages of 0, 3.75, 7.5, and 11.25 mg/kg/day. Decreases in body weight

Table V-8. Summary of Histopathological Findings in Rats Fed Oxamyl for 2 Years

Tissue/finding	Incidence at dietary level (ppm)					
	0	0	150	0	0	150
	Males			Females		
Heart: polyarteritis	10/33 (33) ^a	14/30 (47)	5/30 (17)	1/29 (3)	3/30 (10)	0/30 (0)
Bone marrow hyperplasia	3/30 (10)	5/30 (17)	4/30 (13)	14/29 (48)	18/30 (60)	9/30 (30)
Liver: focal necrosis microgranuloma	2/30 (7) 2/30 (7)	4/30 (13) 7/30 (23)	2/30 (7) 10/30 (33)*	4/29 (14) 6/29 (21)	2/30 (7) 9/30 (30)	2/30 (7) 15/30 (50)*
Mammary tumor ^b	0/30 (0)	0/30 (0)	0/30 (0)	16/29 (55)	20/30 (67)	10/30 (33)
Pituitary tumor ^b	7/30 (23)	8/30 (27)	10/30 (33)	15/29 (52)	17/30 (57)	11/30 (37)
Adrenal tumor ^b	1/30 (3)	2/30 (7)	4/30 (13)	3/29 (10)	1/30 (3)	1/30 (3)

^aNumber of animals affected/number of animals examined (% incidence).

^bMore specific information of the tumor type was not reported.

*These values were determined to be significantly different from combined control values ($p < 0.05$) after recalculation by Dynamac Corp. using Fischer's Exact test.

SOURCE: Adapted from Sherman et al. (1972).

(sporadically significant) in the 50- and 75-ppm groups were noted (see Section V.B.2.) Histopathological examination revealed no significant increases in tumor incidence in test groups compared to controls. A summary of the tumor data is presented in Table V-9. Tumors observed were those commonly found in aging animals and were not considered to be attributable to oxamyl administration. The incidences of hepatomas were 11 and 25% for control males and males fed 150 ppm, respectively, for mice surviving to terminal sacrifice; no hepatomas were observed in females. Lung adenomas occurred at incidences of 22 and 23% for control males and males fed 150 ppm, respectively, and 0 and 3% in control and high-dose females, respectively, for mice surviving to termination of the study. There were no significant increases in tumor incidence in test groups compared to controls. Oxamyl was not carcinogenic in mice under the conditions of this study.

F. SUMMARY

Oxamyl has been shown to be extremely toxic to laboratory animals following acute oral, intraperitoneal, or inhalation exposure. Acute LD₅₀ values in rats ranged from 2.5 mg/kg for oral ingestion to 4.0 mg/kg after ip injection. Mortality occurred immediately after dosing, and signs of cholinesterase inhibition such as salivation, fasciculation, and tremors were observed prior to death. No delayed deaths occurred. Cholinesterase inhibition appears to be the major mechanism of toxicity following oxamyl administration. Administration of atropine after treatment with lethal doses of oxamyl prevented mortality and cholinesterase inhibition in rats. Dermal absorption of oxamyl (in solution) appears to be limited. The acute dermal LD₅₀ for rabbits was 740 mg/kg. Clinical signs of cholinesterase inhibition were observed prior to death, and mortalities

Table V-9. Summary of Tumor Data From Mice Fed Oxamyl for 2 Years

Site/tumor	Incidence ^a at dietary level (ppm)					
	0	25	50	75	0	75
	Males			Females		
Animals found dead or sacrificed moribund						
Kidney: reticular cell sarcoma adenoma	0(0) 0(0)	0(0) 0(0)	0(0) 0(0)	0(0) 0(0)	3(7) 0(0)	0(0) 1(2)
Liver: hepatocellular carcinoma hepatoma	0(0) 2(5)	0(0) 2(5)	0(0) 4(8)	0(0) 2(4)	0(0) 0(0)	0(0) 0(0)
Lung: adenoma	7(18)	1(2)	2(4)	3(7)	2(4)	1(2)
Mammary gland: adenocarcinoma	0(0)	0(0)	0(0)	0(0)	1(2)	0(0)
Animals surviving to terminal sacrifice						
Kidney: reticular cell sarcoma adenoma	1(3) 0(0)	0(0) 0(0)	0(0) 1(3)	1(3) 1(3)	0(0) 0(0)	0(0) 0(0)
Liver: hepatocellular carcinoma hepatoma	2(5) 4(11)	1(3) 6(18)	0(0) 5(17)	0(0) 8(25)	0(0) 0(0)	0(0) 0(0)
Lung: adenoma	8(22)	11(32)	5(17)	7(23)	0(0)	1(3)
Mammary gland: adenocarcinoma	0(0)	0(0)	0(0)	0(0)	1(3)	0(0)

^aNumber of animals affected (% incidence); % incidence = $\frac{\text{number of animals affected}}{\text{number of tissues examined}}$

SOURCE: Adapted from Snyder (1980).

usually occurred within 4.5 hours postadministration. Histopathological examination of tissues did not reveal any abnormalities after acute exposure.

Oxamyl is also highly toxic to rats and mice following long-term oral exposure. Rats fed 100 ppm (6.0 to 7.0 mg/kg/day) for 90 days exhibited significant decreases in body weight gains compared to controls. Decreases in body weight occurred in 28 days for male rats ingesting oxamyl at 100 or 150 ppm (5.0 and 7.5 mg/kg/day). In this study, clinical signs of cholinesterase inhibition and severe weight loss were observed in rats fed 500 ppm for 2 days. No target organs were identified. Histopathological examination of tissues did not reveal any abnormalities attributable to oxamyl ingestion.

Similarly, decreases in body weight gain were observed in rats fed 100 or 150 ppm (5.0 and 7.5 mg/kg/day) of oxamyl for 2 years. Rats ingesting 150 ppm did not exhibit overt clinical signs of cholinesterase inhibition. However, cholinesterase activity in blood was lower in females after 4 days and in males after 8 days of exposure to oxamyl at 150 ppm. The type, onset, and distribution of neoplastic and nonneoplastic lesions were unaffected by ingestion of oxamyl. Tumor incidences and types were comparable between controls and mice fed 150 ppm.

Mice fed oxamyl at 50 ppm (8.7 to 10.8 mg/kg/day) for 2 years exhibited decreases in body weight gain, particularly in the first 6 months of study. In this study, excessive mortality and decreases in body weight were observed in mice fed 100 ppm during the first month of study. This necessitated reduction of the 100-ppm dietary level to 75 ppm. Histopathological findings were comparable between control and test groups. There were no compound-related increases in incidence or type of neoplastic or nonneoplastic lesions.

Dogs fed diets containing up to 150 ppm of oxamyl for 90 days did not exhibit any signs of toxicity compared to control animals. Dogs fed 150 ppm of

oxamyl for 2 years exhibited increases in serum alkaline phosphatase activity and cholesterol levels, suggesting some effect on the liver; however, histopathological examination of the liver and other tissues did not reveal any abnormalities. No differences in body weights, food consumption, clinical signs, or hematological parameters were observed in dogs ingesting up to 150 ppm of oxamyl.

Ingestion of up to 150 ppm of oxamyl for 2 years did not affect the longevity of rats, mice, or dogs. Oxamyl was not considered to be carcinogenic in rats or mice following chronic exposure to 150 or 75 ppm of oxamyl, respectively, in the diet. This is supported by the negative results of several in vitro mutagenicity assays.

The teratogenicity and reproductive toxicity of oxamyl were studied in rats and rabbits. A teratogenicity study in rats revealed that, although maternal toxicity evidenced by decreased body weight gain was observed in pregnant rats fed oxamyl at 100 ppm (8.2 mg/kg/day), no increase in fetal variations or malformations were noted in oxamyl-treated groups fed up to 300 ppm (20.5 mg/kg/day) compared to controls. Similarly, in pregnant rabbits given oral doses of oxamyl at 2 mg/kg/day, decreases in maternal body weight gain were noted during the treatment period (day 6-15 of gestation). No compound-related effects on the fetuses were noted. Therefore, oxamyl is not considered to be teratogenic in rats or rabbits.

Developmental toxicity of oxamyl was demonstrated in both one- and three-generation reproduction studies in rats by decreases in the litter size of dams fed oxamyl at 100 ppm (6.2 to 7 mg/kg/day). In addition, reductions were observed in the body weights of weanlings from dams fed 100 ppm of oxamyl.

Parental toxicity was apparent at 100 ppm, as evidenced by decreases in body weight gain of both males and females. Oxamyl did not affect fertility of rats fed up to 150 ppm (9.3 to 10.1 mg/kg/day), and no increases in incidences of variations or malformation in pups from the 150-ppm group were observed.

VI. HEALTH EFFECTS IN HUMANS

No studies were found in the available literature on the effects of oxamyl exposure in humans.

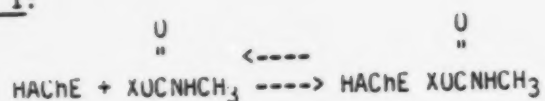
VII. MECHANISMS OF TOXICITY

Specific studies on the mode of action of oxamyl were not found in the available literature. However, the results of the acute animal toxicity studies (cited in Chapter V) indicate that the primary mechanism of toxicity of oxamyl, as is the case with other carbamate insecticides, is cholinesterase inhibition. This is evidenced by the typical clinical signs of cholinesterase inhibition such as salivation, lacrimation, tremors, and fasciculations.

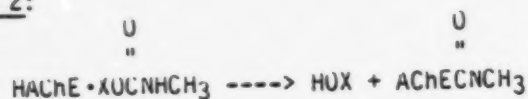
Carbamate insecticides appear to interfere with the cholinesterase transmission of nerve impulses across nerve synapses (Kuhr and Dorough, 1976). Specifically, carbamates enter the synapse, reacting with or inhibiting acetylcholinesterase (AChE), thus preventing the cleavage of the normal substrate, acetylcholine. There is an accumulation of acetylcholine in the nerve synapse causing continued depolarization of the postsynaptic membrane, which results in eventual failure of the peripheral nerve or effector tissue due to prolonged stimulation. Since peripheral cholinesterase synapses control vital functions such as heartbeat and respiration, acute exposure to lethal concentrations of oxamyl causes rapid mortality in animals.

The following equations illustrate the reaction of an N-methylcarbamate insecticide with AChE. This is also the mechanism for dimethyl carbamate and organophosphorus insecticides (Kuhr and Dorough, 1976).

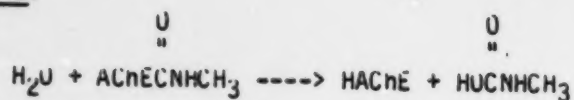
Step 1:



Step 2:



Step 3:



The enzyme couples with the insecticide to form an intermediate complex (Step 1), which can dissociate or decompose into a stable carbamylated enzyme (Step 2) plus a leaving group (the parent phenol, naphthal or oxime). The carbamylated enzyme then hydrolyzes to generate free enzyme and methylcarbamic acid (Step 3). Thus, the reaction does not result in destruction of AChE. However, hydrolysis of the insecticide molecule occurs. Normally (without the presence of the insecticide), AChE cleaves acetylcholine according to the above reaction very rapidly. In the presence of the insecticide (during poisoning), however, there is competition between the insecticide and acetylcholine for an active site on the enzyme. Studies on the kinetics of either reaction have shown that carbamates in general have greater affinity for AChE than acetylcholine (O'Brien et al., 1966; Reiner and Aldridge, 1967). Once attachment occurs, the insecticide "ties up" or inhibits the enzyme, since the reactions in Steps 2 and 3 are much slower for the enzyme-insecticide complex than for the acetylcholine-enzyme complex. The half-life for decarbamylation is approximately 30 to 40 minutes (Reiner and Aldridge, 1967).

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

The quantification of toxicological effects of a chemical consists of an assessment of noncarcinogenic and carcinogenic effects. Chemicals that do not produce carcinogenic effects are believed to have a threshold dose below which no adverse, noncarcinogenic health effects occur, whereas carcinogens are assumed to act without a threshold.

A. PROCEDURES FOR QUANTIFICATION OF TOXICOLOGICAL EFFECTS

1. Noncarcinogenic Effects

In the quantification of noncarcinogenic effects, a Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI), is calculated. The RfD is an estimate of a daily exposure of the human population that is likely to be without appreciable risk of deleterious health effects, even if exposure occurs over a lifetime. The RfD is derived from a No-Observed-Adverse-Effect Level (NOAEL), or Lowest-Observed-Adverse-Effect Level (LOAEL), identified from a subchronic or chronic study, and divided by an uncertainty factor (UF). The RfD is calculated as follows:

$$\text{RfD} = \frac{(\text{NOAEL or LOAEL})}{\text{Uncertainty factor}} = \text{--- mg/kg bw/day}$$

Selection of the uncertainty factor to be employed in the calculation of the RfD is based on professional judgment while considering the entire data base of toxicological effects for the chemical. To ensure that uncertainty factors are selected and applied in a consistent manner, the Office of Drinking Water (ODW) employs a modification to the guidelines proposed by the National Academy of Sciences (NAS, 1977, 1980) as follows:

- o An uncertainty factor of 10 is generally used when good chronic or subchronic human exposure data identifying a NOAEL are available and are supported by good chronic or subchronic toxicity data in other species.
- o An uncertainty factor of 100 is generally used when good chronic toxicity data identifying a NOAEL are available for one or more animal species (and human data are not available), or when good chronic or subchronic toxicity data identifying a LOAEL in humans are available.
- o An uncertainty factor of 1,000 is generally used when limited or incomplete chronic or subchronic toxicity data are available, or when good chronic or subchronic toxicity data identifying a LOAEL, but not a NOAEL, for one or more animal species are available.

The uncertainty factor used for a specific risk assessment is based principally on scientific judgment rather than scientific fact, and accounts for possible intra- and interspecies differences. Additional considerations not incorporated in the NAS/ODW guidelines for selection of an uncertainty factor include the use of a less-than-lifetime study for deriving an RfD, the significance of the adverse health effect, and the counterbalancing of beneficial effects.

From the RfD, a Drinking Water Equivalent Level (DWEL) can be calculated. The DWEL represents a medium-specific (i.e., drinking water) lifetime exposure at which adverse, noncarcinogenic health effects are not expected to occur. The DWEL assumes 100% exposure from drinking water. The DWEL provides the non-carcinogenic health effects basis for establishing a drinking water standard. From ingestion data, the DWEL is derived as follows:

$$DWEL = \frac{RfD \times (\text{body weight in kg})}{\text{Drinking water volume in L/day}} = \text{--- mg/L (--- ug/L)}$$

where:

Body weight = assumed to be 70 kg for an adult.

Drinking water volume = assumed to be 2 L per day for an adult.

In addition to the RfD and the DWEL, Health Advisories (HAs) for exposures of shorter duration (One-day, Ten-day, and Longer-term HAs) are determined. The HA values are used as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur. The HAs are calculated using a similar equation to the RfD and DWEL; however, the NOAELs or LOAELs are identified from acute or subchronic studies. The HAs are derived as follows:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (bw)}{(\text{--- L/day}) \times (UF)} = \text{--- mg/L (--- ug/L)}$$

Using the above equation, the following drinking water HAs are developed for noncarcinogenic effects:

1. One-day HA for a 10-kg child ingesting 1 L water per day.
2. Ten-day HA for a 10-kg child ingesting 1 L water per day.
3. Longer-term HA for a 10-kg child ingesting 1 L water per day.
4. Longer-term HA for a 70-kg adult ingesting 2 L water per day.

The One-day HA calculated for a 10-kg child assumes a single acute exposure to the chemical and is generally derived from a study of less than 7 days' duration. The Ten-day HA assumes a limited exposure period of 1 to 2 weeks and is generally derived from a study of less than 30 days' duration. A Longer-term HA is derived for both a 10-kg child and a 70-kg adult and assumes an

exposure period of approximately 7 years (or 10% of an individual's lifetime). A Longer-term HA is generally derived from a study of subchronic duration (exposure for 10% of an animal's lifetime).

2. Carcinogenic Effects

The EPA categorizes the carcinogenic potential of a chemical, based on the overall weight of evidence, according to the following scheme:

- o Group A: Known Human Carcinogen. Sufficient evidence exists from epidemiology studies to support a causal association between exposure to the chemical and human cancer.
- o Group B: Probable Human Carcinogen. Sufficient evidence of carcinogenicity in animals with limited (Group B1) or inadequate (Group B2) evidence in humans.
- o Group C: Possible Human Carcinogen. Limited evidence of carcinogenicity in animals in the absence of human data.
- o Group D: Not Classified as to Human Carcinogenicity. Inadequate human and animal evidence of carcinogenicity or for which no data are available.
- o Group E: Evidence of Noncarcinogenicity for Humans. No evidence of carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.

If toxicological evidence leads to the classification of the contaminant as a known, probable, or possible human carcinogen, mathematical models are

used to calculate the estimate of excess cancer risk associated with the ingestion of the contaminant in drinking water. The data used in these estimates usually come from lifetime exposure studies in animals. To predict the risk for humans from animal data, animal doses must be converted to equivalent human doses. This conversion includes correction for noncontinuous exposure, less-than-lifetime studies, and for differences in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average adult human body weight is 70 kg and that the average water consumption of an adult human is 2 liters of water per day.

For contaminants with a carcinogenic potential, chemical levels are correlated with a carcinogenic risk estimate by employing a cancer potency (unit risk) value together with the assumption for lifetime exposure via ingestion of water. The cancer unit risk is usually derived from a linearized multistage model with a 95% upper confidence limit providing a low-dose estimate; that is, the true risk to humans, while not identifiable, is not likely to exceed the upper limit estimate and, in fact, may be lower. Excess cancer risk estimates may also be calculated using other models such as the one-hit, Weibull, logit, and probit. There is little basis in the current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than any others. Because each model is based on differing assumptions, the estimates that are derived for each model can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of cancer risk rate levels has an inherent uncertainty due to the systematic and random errors in scientific measurement. In most cases, only studies using

laboratory animals have been performed. Thus, there is uncertainty when the data are extrapolated to humans. When developing cancer risk rate levels, several other areas of uncertainty exist, such as the incomplete knowledge concerning the health effects of contaminants in drinking water; the impact of the laboratory animal's age, sex, and species; the nature of the target organ system(s) examined; and the actual rate of exposure of the internal targets in laboratory animals or humans. Dose-response data usually are available only for high levels of exposure, not for the lower levels of exposure closer to where a standard may be set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

B. QUANTIFICATION OF NONCARCINOGENIC EFFECTS FOR OXAMYL

1. One-day Health Advisory

No suitable data were found in the literature for calculation of the One-day HA for oxamyl. Therefore, a conservative estimate of the One-day HA of 200 ug/L, the Longer-term HA for a 10-kg child, was substituted as the One-day HA.

2. Ten-day Health Advisory

No data found in the literature were appropriate for calculation of the Ten-day HA. Therefore, the Longer-term HA for a 10-kg child of 200 ug/L can be substituted as a conservative estimate of the Ten-day HA.

3. Longer-term Health Advisory

Two subchronic feeding studies were considered for derivation of the Longer-term HA (Table VIII-1). In a 90-day feeding study conducted by Haskell Laboratory (Kennedy, 1986b; Sherman et al., 1972) in which Crl:CD rats were fed diets

Table VIII-1. Summary of Subchronic Feeding Studies Considered in the Development of the Longer-term Health Advisory for Oxamyl

Reference	Species (sex)	Route	Duration (days)	Dose (ppm)	Effects
Kennedy (1986b) ^a	Rat (M/F)	dietary	90	50	NOAEL
				100	Decreased body weight
				150	Decreased body weight
Kennedy (1986b)	Dog (M/F)	dietary	90	50	NOAEL
				100	
				150	

^aPreviously reported by Sherman et al. (1972).

containing 0, 50, 100, or 150 ppm of oxamyl at equivalent doses of approximately 2.5, 5.0, and 7.5 mg/kg/day (U.S. EPA, 1987), the NOAEL was 50 ppm (approximately 2.5 mg/kg/day), based on decreases in body weight of males and females fed 100 or 150 ppm of oxamyl. In the second 90-day feeding study conducted at Hazleton Laboratories (Kennedy, 1986b), beagles were fed diets containing 0, 50, 100, or 150 ppm (approximately equivalent to doses of 1.3, 2.5, or 3.8 mg/kg/day). The NOAEL for this study was identified as 3.8 mg/kg/day, the highest dose tested, based on lack of change in any parameter measured including body weight, food consumption, hematology, clinical chemistry, or histopathological examination.

The 90-day feeding study in rats was selected for calculation of the Longer-term HA because it was of appropriate duration, dose levels appeared to be adequately chosen, and the study was adequately conducted.

The Longer-term HA for a 10-kg child is calculated as follows:

$$\frac{(2.5 \text{ mg/kg/day}) (10 \text{ kg})}{(1 \text{ L/day}) (100)} = 0.25 \text{ mg/L (rounded to 200 ug/L)}$$

where:

2.5 mg/kg/day = NOAEL, based on the absence of decreases in body weight of rats.

10 kg = assumed body weight of a child.

1 L/day = assumed daily water consumption of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

The Longer-term HA for a 70-kg adult is calculated as follows:

$$\frac{(2.5 \text{ mg/kg/day}) (70 \text{ kg})}{(2 \text{ L/day}) (100)} = 0.875 \text{ mg/L (rounded to 900 ug/L)}$$

where:

2.5 mg/kg/day = NOAEL, based on the absence of decreases in body weight of rats.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

4. Reference Dose and Drinking Water Equivalent Level

Three chronic feeding studies were considered for derivation of the Reference Dose (RfD) and Drinking Water Equivalent Level (DWEL) (Table VIII-2). In a study conducted by Haskell Laboratory (Kennedy, 1986b; Sherman et al., 1972), Crl:CD rats were fed diets containing 0, 50, 100, or 150 ppm of oxamyl for 2 years. These levels were approximately equal to doses of 0, 2.5, 5.0, and 7.5 mg/kg/day (U.S. EPA, 1987). Significant decreases ($p \leq 0.05$) in body weights were noted in males and females fed oxamyl at 5.0 and 7.5 mg/kg/day. Cholinesterase activity was significantly decreased in females fed 7.5 mg/kg/day after 4 days and in males fed 7.5 mg/kg/day after 8 days of ingestion of oxamyl. However, these levels were within normal range for the remainder of the study. The NOAEL for this study was identified as 50 ppm (2.5 mg/kg/day).

In a 2-year chronic feeding study in dogs, also conducted at Haskell Laboratory, (Kennedy, 1986b; Sherman et al., 1972) beagles were fed diets containing oxamyl at levels of 0, 50, 100, or 150 ppm (equivalent to approximately 0, 1.3, 2.5, or 3.8 mg/kg/day, respectively). Body weights, clinical observations, hematological and urinalysis parameters, and histopathological evaluations were comparable between control and test groups. Alkaline

Table VIII-2. Summary of Chronic Feeding Studies Considered in the Development of the Reference Dose and Drinking Water Equivalent Level for Oxamyl

Reference	Species (sex)	Route	Duration (years)	Dose (ppm)	Effects
Kennedy (1986b)a	Rat (M/F)	dietary	2	50	NOAEL
				100	Decreases in body weight
				150	Decreases in body weight
Kennedy (1986b)	Mouse (M/F)	dietary	2	25	NOAEL
				50	Decreases in body weight
				75	Decreases in body weight, decreases in hematological parameters
Kennedy (1986b)	Dog (M/F)	dietary	2	50	--
				100	NOAEL
				150	Decreases in serum alkaline phosphatase activity and cholesterol levels

aPreviously reported by Sherman et al. (1972).

phosphatase activity and cholesterol levels were increased in dogs at the 150-ppm dose level compared to controls. The NOAEL for this study was 100 ppm (2.5 mg/kg/day) (Kennedy, 1986b).

CD-1 mice were fed diets containing 0, 25, 50, or 75 ppm (equivalent to doses of 0, 3.5, and 11.25 mg/kg/day, respectively). Significant decreases ($p < 0.05$) in the body weights of animals fed 50 or 75 ppm of oxamyl were sporadically noted only in the first 6 months of exposure, after which body weights of mice in the 50- and 75-ppm groups were comparable to controls. Hemoglobin, hematocrit levels, and red blood cell counts were significantly decreased ($p < 0.01$) compared to controls after 4 weeks of exposure. However, these values were within normal range for the remainder of the study. The NOAEL for this study was 25 ppm (3.5 mg/kg/day).

The rat feeding study conducted at Haskell Laboratory was selected for calculation of the RfD and DWEL because it was a comprehensive, adequately run study of appropriate duration. In addition, the NOAEL for this study (2.5 mg/kg/day) was supported by NOAEL values of 2.5 and 3.5 mg/kg/day identified in the chronic dog and mouse studies, respectively.

The DWEL for a 70-kg adult is calculated as follows:

Step 1: Determination of the RfD

$$\text{RfD} = \frac{(2.5 \text{ mg/kg/day})}{100} = 0.025 \text{ mg/kg/day (25 ug/kg/day)}$$

where:

2.5 mg/kg/day = NOAEL, based on absence of changes in body weight in rats.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the DWEL

$$\text{DWEL} = \frac{(0.025 \text{ mg/kg/day}) (70 \text{ kg})}{2 \text{ L/day}} = 0.875 \text{ mg/L (900 ug/L)}$$

where:

0.025 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

C. QUANTIFICATION OF CARCINOGENIC EFFECTS FOR OXAMYL

Two studies were considered for derivation of carcinogenic risk estimates for oxamyl. In a 2-year feeding study in which Crl:CD rats were fed oxamyl at levels of 0, 50, 100, or 150 ppm (equivalent to daily doses of 0, 2.5, 5.0, and 7.5 mg/kg/day) systemic toxicity in the form of reduced body weights was noted in males and females fed 100 or 150 ppm of oxamyl. Histopathologic evaluation of tissues from control and high-dose animals revealed no increases in incidence of neoplastic or nonneoplastic lesions attributable to oxamyl ingestion (see Section V.E. and Table V-8) (Kennedy, 1986b; Sherman et al., 1972). A few deficiencies were noted in this study. Numbers of animals tested and examined histologically (36/sex/dose) were not adequate according to current standards. In addition, possible target organs such as the liver and reproductive organs were apparently not examined histologically in all groups.

Similar results were obtained in a 2-year feeding study in CD-1 mice fed 0, 25, 50, or 75 ppm of oxamyl (equivalent to daily doses of 0, 3.5, 7.5, and 11.25 mg/kg/day, respectively). Decreases in body weight were noted in males and females fed 50 or 75 ppm of oxamyl, particularly in the first 6 months of study. As in the rat study, ingestion of up to 75 ppm (11.25 mg/kg/day) of

oxamyl did not result in increased incidences in type or frequency of tumors in mice (see Section V.E. and Table V-9) (Kennedy, 1986b; Snyder, 1980).

The available data suggest that orally ingested oxamyl is not carcinogenic to laboratory animals. Therefore, no calculation of excess cancer risk was performed.

D. SUMMARY

Table VIII-3 summarizes the HA and DWEL values for oxamyl.

Oxamyl may be classified in Group E: Evidence of Noncarcinogenicity for Humans, based on the results of at least two adequate animal tests in different species in which no evidence of carcinogenicity was obtained (U.S. EPA, 1987).

Table VIII-3. Summary of Quantification of Toxicological Effects for Oxamyl

Value	<u>Drinking water concentration</u> (ug/L)	Reference
One-day HA for 10-kg child	-- ^a	--
Ten-day HA for 10-kg child	-- ^a	--
Longer-term HA for 10-kg child	900	Kennedy (1986b)
Longer-term HA for 70-kg adult	900	Kennedy (1986b)
DWEL (100% from drinking water)	900	Kennedy (1986b)
Excess cancer risk (10 ⁻⁶)	--	

^aThese numbers were based on the Longer-term HA because of lack of appropriate data for derivation of the One- and Ten-day HAs.

The Longer-term HA value is recommended as a conservative estimate of the One-day and Ten-day HA values.

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